

Exhibit N



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS



June 21, 2022

Robert Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: U.S. Food and Drug Administration actions related to mifepristone

Dear Dr. Califf:

On behalf of the American College of Obstetricians and Gynecologists (ACOG), representing more than 60,000 physicians and partners dedicated to advancing women's health and individuals seeking obstetric and gynecologic care, and the American Medical Association, we write to express our appreciation for the support demonstrated by the U.S. Food and Drug Administration (FDA) in response to the needs of individuals seeking reproductive care. Respectfully, we request that additional actions are taken to improve access to quality women's health care. In anticipation of the crisis to abortion access that is expected to follow the United States Supreme Court's decision in the *Dobbs v. Jackson Women's Health Organization* case, we strongly urge you to prioritize the following evidence-based decisions that will increase access to mifepristone:

- Reconsider the implementation of the Risk Evaluation and Mitigation Strategies (REMS) and Elements to Assure Safe Use (ETASU) requirements for mifepristone and ensure the process does not add unnecessary and unmitigated burdens for physicians, patients, and pharmacies; and
- Explicitly preempt state laws relating to mifepristone that are not evidence-based, that interfere with the medically necessary and appropriate use of a safe and effective drug, and that frustrate the FDA's regulatory decisions relating to mifepristone, and that have inconsistent policies and laws restricting access to mifepristone.

Mifepristone is Safe and Effective

Mifepristone is a safe, effective, and important component of treatment and management for early pregnancy loss (i.e., spontaneous abortion, miscarriage, missed abortion) and induced abortion. Mifepristone has been used by over 3 million women in the United States since FDA approval in 2000, and robust evidence exists regarding the safety of mifepristone for medication-induced abortion.^{1,2,3,4}

Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies and affects approximately 1 million women in the U.S. annually.^{5,6} Recent evidence demonstrates that mifepristone significantly improves the safe and effective medical management of early pregnancy loss when taken as part of a two-medication regimen.^{7,8} A 2018 randomized controlled trial demonstrated that people who received mifepristone in addition to misoprostol experienced increased rates of complete expulsion and required fewer procedures compared to those who received misoprostol alone.⁹ Therefore, we ask that the FDA modify the mifepristone label indicating that mifepristone is approved for the use of miscarriage management.

As referenced in ACOG clinical guidance, the evidence supports medication abortion as a safe and effective method of providing abortion care.¹⁰ Barriers to accessing mifepristone do not make care safer, are not based on medical evidence, and create barriers to patient access to essential reproductive health care.^{11, 12} Abortion care is time-sensitive: delays in care increase risk to patients and potentially results in an abortion being completely inaccessible.¹³ Research conducted during the COVID-19 pandemic demonstrates that when enforcement of the in-person dispensing requirement for mifepristone was suspended, abortion through telehealth contact and mailed medications was safe.¹⁴

According to reaffirmed ACOG guidance, second-trimester abortion is safely accomplished through medical induction or medical abortion, especially when compared with other methods.¹⁵ Mifepristone followed in 24–48 hours by misoprostol is the most effective regimen for second-trimester medical abortion.¹⁶ In fact, that regimen is up to 91% successful within 24 hours of initiation of misoprostol, and outcomes include a significantly shorter induction interval and fewer adverse effects than misoprostol alone.¹⁷

FDA Preemption of State Laws that Restrict Access to Mifepristone

There are currently nineteen states that require a physician to be present upon delivery of mifepristone; two states have made it illegal to use mifepristone at earlier gestation ages than the label allows.¹⁸ Neither of these state restrictions are evidence-based.

Mifepristone is approved by the FDA to be used with misoprostol for medication abortion through 70 days of gestation.^{19,20} In 2016, the FDA expanded the gestational age limit from 49 to 70 days (10 weeks) to better correspond with recently published evidence.^{21,22} The 2015 systematic review reported average effectiveness rates of 96.7% in the 8th week, 95.2% in the 9th week, and 93.1% in the 10th week. Subsequently, evidence-based guidelines concluded that mifepristone followed in 24–48 hours by misoprostol is the most effective regimen for second-

trimester medical abortion.²³ Currently, strong evidence supports the use of the mifepristone regimen through 77 days gestation, and multi-center study published in 2022 found that many physicians offer mifepristone up to 77 days.^{24,25}

Experts, including ACOG, and the growing body of scientific evidence, demonstrate that the FDA regulations should preempt those state laws and prevent state lawmakers from imposing restrictions that are not evidence-based, that interfere with the medically necessary and appropriate use of a safe and effective drug, that frustrate access to necessary care and are inconsistent with the FDA's regulatory decisions relating to mifepristone.

Revisit or Remove the Risk Evaluation and Mitigation Strategies (REMS) and Elements to Assure Safe Use (ETASU) Requirements for Mifepristone

Recognizing the accomplishments of the FDA in modifying the REMS for mifepristone, we continue to urge the FDA to remove or make further changes to the REMS and ETASU requirements to allow obstetrician–gynecologists and other physicians to deliver the highest quality care for their patients. While the FDA updated the REMS for mifepristone in December 2021, the REMS for mifepristone still requires use of a provider agreement form, a patient agreement form and dispensing from a pharmacy certified by the drug distributors. The agency and manufacturers have not yet defined the pharmacy certification process; however, we are concerned that this unnecessary hurdle could serve as a deterrent to pharmacies' decisions to stock and dispense mifepristone. To increase access to mifepristone, we ask that, at a minimum, the FDA simplify the pharmacy certification process, eliminate the requirement for patients to sign a form to get the drug, lift the requirement that prescribers acquire a certification from the manufacturer, and evaluate adding protections for availability of mifepristone via telehealth.

Failure to Improve Access to Mifepristone Will Threaten to Exacerbate the Maternal Mortality Crisis

The United States leads the developed world in rates of maternal mortality. In 2020, the most recent year for which data is available, there were 23.8 deaths per 100,000 live births, up from 20.1 in 2019.²⁶ Alarmingly, the maternal mortality rate for Black women was 55.3 deaths per 100,000 live births, 2.9 times the rate for White women, and rates significantly increased for both Black and Hispanic women.²⁷ The rising maternal mortality rates and persistent racial disparities in maternal outcomes are unacceptable. However, without sufficient access to abortion care, including mifepristone, these figures are certain to climb.

Current data support an association between restricted access to safe and legal abortion and higher rates of maternal morbidity and mortality, with already vulnerable populations experiencing the greatest burden.^{28,29,30} At just 0.3 deaths per 100,000 abortions performed at or before 8 weeks, the mortality rate associated with abortion is significantly lower than the mortality rate associated with childbirth.³¹ A lack of access to mifepristone will result in more pregnancies, including high-risk pregnancies, which is associated with the much higher maternal mortality rates described above. A recent study estimated a total, nationwide abortion ban would increase pregnancy-related deaths by 7% in the first year and 21% in subsequent years, including a 33% increase for Black people.³²

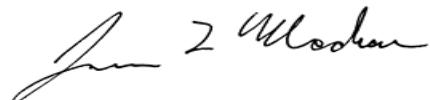
Furthermore, research suggests that a lack of abortion access carries the risk of adverse physical outcomes. The harm of mifepristone restrictions is also more pronounced for patients with medical conditions for which a medication abortion may be preferable to uterine aspiration. Such examples include uterine fibroids that significantly distort the cervical canal or uterine cavity, congenital uterine anomalies, or introital scarring related to infibulation.³³ Patients with asthma are candidates for medication abortion because misoprostol does not cause bronchoconstriction and actually acts as a weak bronchodilator.³⁴ Carrying a pregnancy to term is also associated with mental health conditions. A 2017 study found women who were denied abortions experienced more symptoms of anxiety, lower self-esteem, and lower life satisfaction after one week than their counterparts who obtained abortions.³⁵ Perinatal depression, which includes major and minor depressive episodes that occur during pregnancy or in the first 12 months after delivery, is one of the most common medical complications during pregnancy and the postpartum period, affecting one in seven.³⁶ Finally, restrictions on the use of telemedicine have a disproportionate effect on rural people's access to abortion, who are forced to travel substantially greater distances outside of their communities than nonrural women for care.³⁷

Thank you for your attention to this critical issue and your continued partnership with us. Your commitment and dedication to advancing women's health and individuals receiving obstetric and gynecologic care is recognized and appreciated. Should you have any questions, please contact Rebecca Lauer, Manager, Federal Affairs, at rlauer@acog.org.

Sincerely,



Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists



James L. Madara, MD
CEO, Executive Vice President
American Medical Association

cc: The Honorable Joseph R. Biden, Jr.
The Honorable Kamala D. Harris

¹ Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at <https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications>.

² Cleland K, Smith N. Aligning mifepristone regulation with evidence: Driving policy change using 15 years of excellent safety data. *Contraception*. 2015;92(3):179-181. doi:10.1016/j.contraception.2015.06.016.

³ Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*. 2017;376(8):790-794.

⁴ Song LP, Tang SY, Li CL, Zhou LJGYK, Mo XT. Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol. *J Obstet Gynaecol Res*. 2018;44(9):1705-1711. doi:10.1111/jog.13716.

⁵ Early pregnancy loss. Practice Bulletin No. 150. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;125:1258-67.

⁶ Ventura SJ, Curtin SC, Abma JC, Henshaw SK. Estimated pregnancy rates and rates of pregnancy outcomes for the United States, 1990-2008. *Natl Vital Stat Rep* 2012;60(7):1-21.

⁷ Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. *N Engl J Med* 2018;378:2161-70.

⁸ Westhoff CL. A Better medical regimen for the management of miscarriage. *N Engl J Med* 2018;378:2232-3.

⁹ Schreiber CA , Creinin MD , Atrio J , Sonalkar S , Ratcliffe SJ , Barnhart KT . Mifepristone pretreatment for the medical management of early pregnancy loss . *N Engl J Med* 2018; 378:2161-70.

¹⁰ Medication abortion up to 70 days of gestation. ACOG Practice Bulletin No. 225. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2020;136:e31-47.

¹¹ Grossman D, Grindlay K, Altshuler AL, Schulkin J. Induced abortion provision among a national sample of obstetrician-gynecologists. *Obstet Gynecol* 2019;133:477-83.

¹² Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M, et al. Sixteen years of overregulation: time to unburden mifeprex. Mifeprex REMS Study Group. *N Engl J Med* 2017;376:790-4.

¹³ Joint Statement on Abortion Access During the COVID-19 Outbreak. March 18, 2020. Available at: <https://www.acog.org/news/news-releases/2020/03/joint-statement-on-abortion-access-during-the-covid-19-outbreak>.

¹⁴ Kerestes C, Murayama S, Tyson J, Natavio M, Seamon E, Raidoo S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021.

¹⁵ Second-trimester abortion. Practice Bulletin No. 135. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:1394–1406.

¹⁶ Ibid.

¹⁷ Ibid.

¹⁸ Guttmacher Institute. Medication Abortion. Available at: <https://www.guttmacher.org/state-policy/explore/medication-abortion>. Retrieved June 16, 2022.

¹⁹ Second-trimester abortion. Practice Bulletin No. 135. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:1394–406.

²⁰ World Health Organization. Medical management of abortion . Geneva: WHO; 2018. Available at: <https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1>. Retrieved June 16, 2022.

²¹ Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. *Contraception* 2015;92:197-9.

²² Chen MJ, Creinin MD. Mifepristone with buccal misoprostol for medical abortion: a systematic review. *Obstet Gynecol* 2015;126:12-21.

²³ Second-trimester abortion. Practice Bulletin No. 135. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:1394–406.

²⁴ 3. Dzuba IG, Chong E, Hannum C, et al. A non-inferiority study of outpatient mifepristone-misoprostol medical abortion at 64-70 days and 71-77 days of gestation. *Contraception*. 2020;101(5):302-308.

²⁵ Upadhyay UD, Raymond EG, Koenig LR, et al. Outcomes and Safety of History-Based Screening for Medication Abortion: A Retrospective Multicenter Cohort Study. *JAMA Intern Med*. 2022;182(5):482–491.

²⁶ Hoyert DL. Maternal mortality rates in the United States, 2020. National Center for Health Statistics Health E-Stats. February 23, 2022. doi: <https://dx.doi.org/10.15620/cdc:113967>

²⁷ Ibid.

²⁸ Addante, A.N., et al., *The association between state-level abortion restrictions and maternal mortality in the United States, 1995-2017*. Contraception, 2021. 104(5): p. 496-501.

²⁹ Hawkins, S.S., et al., *Impact of State-Level Changes on Maternal Mortality: A Population-Based, Quasi-Experimental Study*. Am J Prev Med, 2020. 58(2): p. 165-174.

³⁰ Verma, N. and S.A. Shainker, *Maternal mortality, abortion access, and optimizing care in an increasingly restrictive United States: A review of the current climate*. Semin Perinatol, 2020. 44(5): p. 151269.

³¹ Medicaid Coverage of Abortion. Guttmacher Institute. Medicaid Coverage of Abortion. Available at: <https://www.guttmacher.org/evidence-you-can-use/medicaid-coverage-abortion>. Retrieved June 16, 2022.

³² Stevenson, AJ. The Pregnancy-Related Mortality Impact of a Total Abortion Ban in the United States: A Research Note on Increased Deaths Due to Remaining Pregnant. *Demography*. December 1, 2021; 58 (6):2019–2028. doi: <https://doi.org/10.1215/00703370-9585908>.

³³ Second-trimester abortion. Practice Bulletin No. 135. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:1394–406.

³⁴ Ibid.

³⁵ Biggs MA, Upadhyay UD, McCulloch CE, Foster DG. Women's Mental Health and Well-being 5 Years After Receiving or Being Denied an Abortion: A Prospective, Longitudinal Cohort Study. *JAMA Psychiatry*. 2017;74(2):169–178. <https://doi:10.1001/jamapsychiatry.2016.3478>.

³⁶ Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol*. 2005;106:1071–83.

³⁷ Health disparities in rural women. Committee Opinion No. 586. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2014;123:384–8.